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File: PGPB

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TITLE: Oral administration of lactobacillus for the maintenance of health in women during pregnancy and at other life stages, to reduce the risk of urogenital diseases

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## INVENTOR-INFORMATION:

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## RELATED-US-APPL-DATA:

Application 10/317666 is a division-of US application 09/579307, filed May 25, 2000, ABANDONED  
Application is a non-provisional-of-provisional application 60/135955, filed May 25, 1999,

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REPRESENTATIVE-FIGURES: NONE

## ABSTRACT:

The present invention provides methods and compositions for the oral administration of Lactobacillus and/or other probiotic organisms, such as Bifidobacterium, for establishment and maintenance of a healthy urogenital flora. The invention also provides methods and compositions to reduce the risk of disease, including onset of preterm labor due to vaginal and cervical infection. The invention also provides ex vivo methods of restoring healthy gastrointestinal and vaginal flora.

## CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 60/135,955 filed May 25, 1999.

## FIELD OF THE INVENTION

[0002] The present invention provides methods and compositions for the oral

administration of Lactobacillus and/or other probiotic organisms, such as Bifidobacterium, for establishment and maintenance of a healthy urogenital flora. The invention also provides methods and compositions to reduce the risk of disease, including onset of preterm labor due to vaginal and cervical infection.

#### BACKGROUND OF THE INVENTION

[0003] The organisms which constitute the flora of the urogenital tract in females, originate from the gastrointestinal tract. Of the approximately 50 species of microbes which inhabit the vagina, urethra, cervix, perineum and vulva, Lactobacillus and Bifidobacterium represent the most dominant species in healthy women. These organisms dominate the vaginal flora in pre-menopausal women. The ability of these organisms to exist, persist and dominate the flora, is influenced in part by the changing bacterial and nutrient environment of the gastrointestinal tract.

[0004] In post-menopausal women, the normal healthy urogenital flora may also contain lactobacilli, bifidobacteria, or other naturally occurring and non-infectious organisms. However, in this age group, urogenital infections are particularly common, and some studies have suggested that the reduction in estrogen levels causes the depletion of lactobacilli, due in part to reduced amounts of glycogen or mucus which lactobacilli use as nutrients and receptors.

[0005] Organisms, e.g. urogenital pathogens, which cause many urogenital infections, such as yeast vaginitis, bacterial vaginosis and urinary tract infections, originate predominantly in the gastrointestinal tract. In such disease states, the lactobacilli flora are depleted. Urogenital infections predispose many pregnant women to preterm labor and premature birth. In young and aged females alike, a disruption of the urogenital flora leads to an increased risk of sexually transmitted diseases. Thus, establishment and maintenance of a normal, healthy urogenital flora is vitally important to the well-being of females.

[0006] Previous studies have shown that certain lactobacilli organisms possess the ability to interfere with urogenital pathogens. (Reid, et al. (1987) "Examination of strains of lactobacilli for properties which may influence bacterial interference in the urinary tract," J. Urol., 138:330-335; Reid, et al. (1988) "Lactobacillus inhibitor production against E. coli and coaggregation ability with uropathogens," Can. J. Microbiol., 34:344-351). Such lactobacilli can be delivered orally and vaginally to prevent infections. The delivery of bacteria to improve well being is termed probiotics.

#### SUMMARY OF THE INVENTION

[0007] The present invention provides methods and compositions for the establishment and maintenance of a healthy gastrointestinal and urogenital flora. The invention provides lactobacilli or bifidobacteria, which, when taken orally, enhance the flora's ability to out-compete gastrointestinal and urogenital pathogens. From this intestinal niche, the probiotic organisms unexpectedly emerge to naturally colonize the perineum, vulva, vagina and/or urethra and to establish and maintain a normal healthy flora.

[0008] In one aspect of the present invention a method is provided for establishing a healthy gastrointestinal and urogenital flora in females throughout life comprising orally administering a therapeutically effective amount of at least one probiotic organism and a pharmaceutically acceptable carrier. In a further aspect of the method a therapeutically effective amount of a second probiotic organism is administered. Lactobacillus is the preferred probiotic organism. The Lactobacillus is preferably selected from the group consisting of L. rhamnosus, L. acidophilus,

L. fermentum, L. casei, L. reuteri, L. crispatus, L. plantarum, L. paracasei, L. jensenii, L. gasseri, L. cellobiosis, L. brevis, L. delbrueckii, L. helveticus, L. salivarius, L. collinoides, L. buchneri, L. rogosae, or L. bifidum. Bifidobacteria is the preferred second probiotic organism. The Bifidobacterium is preferably selected from the group consisting of B. bifidum, B. breve, B. adolescentis, or B. longum.

[0009] In another aspect of the present invention a prebiotic is administered in conjunction with the probiotic organism.

[0010] In still another aspect of the present invention an ex vivo method is provided for establishing a healthy gastrointestinal and urogenital flora in a females comprising orally administering at least one probiotic organism isolated from said female and a pharmaceutically acceptable carrier. In a further aspect the probiotic organisms are isolated or obtained from the patient.

[0011] In yet another aspect of the present invention a method is provided for maintaining a healthy urogenital flora in females prior to, during and after pregnancy comprising orally administering at least one probiotic organism and a pharmaceutically acceptable carrier. In a further aspect of the method a therapeutically effective amount of a second probiotic organism is administered. Lactobacillus is the preferred first probiotic organism. The Lactobacillus is preferably selected from the group consisting of L. rhamnosus, L. acidophilus, L. fermentum, L. casei, L. reuteri, L. crispatus, L. plantarum, L. paracasei, L. jensenii, L. gasseri, L. cellobiosis, L. brevis, L. delbrueckii, L. helveticus, L. salivarius, L. collinoides, L. buchneri, L. rogosae, or L. bifidum. Bifidobacteria is the preferred second probiotic organism. The Bifidobacterium is preferably selected from the group consisting of B. bifidum, B. breve, B. adolescentis, or B. longum.

[0012] In still another aspect of the present invention an ex vivo method is provided for restoring healthy gastrointestinal and urogenital flora in females in need thereof comprising orally administering at least one probiotic organism isolated from the individual and a pharmaceutically acceptable carrier.

[0013] In another aspect of the present invention, a method is provided for reducing the risk of preterm labor comprising orally administering a therapeutically effective amount of at least one probiotic organism and a pharmaceutically acceptable carrier.

[0014] In another aspect of the present invention, a method is provided for reducing the risk of bacterial vaginosis and bacterial vaginosis pathogens comprising orally administering a therapeutically effective amount of at least one probiotic organism and a pharmaceutically acceptable carrier.

[0015] In still yet another aspect of the present invention a pharmaceutical composition is provided which comprises a probiotic organism and a pharmaceutically acceptable carrier.

[0016] In yet another aspect of the present invention an ex vivo method is provided for maintaining healthy urogenital flora in a newborn comprising orally administering at least one probiotic organism which has been isolated from the newborn or mother or provided from an exogenous source and a pharmaceutically acceptable carrier.

[0017] In a further aspect of the present invention a method is provided for selecting lactobacilli and bifidobacteria useful for improving gastrointestinal and urogenital health comprising detecting an ability to: adhere to gastrointestinal,

vaginal and uroepithelial cells by electrostatic, hydrophobic or specific adhesins including a collagen binding protein; pass through the stomach and reach the small and large intestine; grow and persist in the gastrointestinal and urogenital tracts; inhibit the adhesion of gastrointestinal and urogenital pathogens including organisms which cause urinary tract infection, bacterial vaginosis and yeast vaginitis; coaggregate to form a balanced flora; produce acid and other substances such as hydrogen peroxide and/or bacteriocins and bacteriocin-like compounds which inhibit pathogen growth; produce biosurfactant or related by-products of growth which interfere with adhesion of pathogens to cells and materials; resist antimicrobial agents, such as nonoxynol-9 spermicide; and/or enhance the host's immune function to further maintain a healthy urogenital flora.

#### BRIEF DESCRIPTION OF THE FIGURES

[0018] FIG. 1 is a bar graph which shows viable counts of lactobacilli strains before (white bars) and after (dark bars) 16-hour incubation with FALL-39 (100  $\mu$ mol 1.sup.-1). Mottled bars represent control counts (incubation without peptide). Mean values obtained from three independent experiments are shown.

[0019] FIG. 2 is a surface enhanced laser desorption/ionization (SELDI) mass profile of lactobacillus expression of collagen binding proteins in Lactobacillus acidophilus RC-14; L. rhamnosus GR-1 and L. rhamnosus 36W.

[0020] FIG. 3 is a SELDI mass profile of lactobacillus expression of collagen binding proteins in Lactobacillus acidophilus RC-14 using protein chip PS-1/CN-III.

#### DETAILED DESCRIPTION OF THE INVENTION

[0021] The present invention provides methods and compositions for establishing and maintaining a healthy gastrointestinal and urogenital flora in women throughout the life cycle comprising the administration of probiotic organisms such as Lactobacillus and/or Bifidobacterium and/or a prebiotic compound.

[0022] By "probiotic" is meant an organism which has one or more of the following characteristics, an ability to improving gastrointestinal and urogenital health comprising detecting an ability to: adhere to gastrointestinal, vaginal and uroepithelial cells by electrostatic, hydrophobic or specific adhesins including a collagen binding protein; pass through the stomach and reach the small and large intestine; grow and persist in the gastrointestinal and urogenital tracts; inhibit the adhesion of gastrointestinal and urogenital pathogens including organisms which cause urinary tract infection, bacterial vaginosis and yeast vaginitis; coaggregate to form a balanced flora; produce acid and other substances such as hydrogen peroxide and/or bacteriocins and bacteriocin-like compounds which inhibit pathogen growth; produce biosurfactant or related by-products of growth which interfere with adhesion of pathogens to cells and materials; resist antimicrobial agents, such as nonoxynol-9 spermicide; and/or enhance the host's immune function to further maintain a healthy urogenital flora. A preferred probiotic organism is one or more species of Lactobacillus and extracts or by-products thereof such as proteins or peptides or amino acids.

[0023] The preferred strains of lactobacilli within the scope of this invention are aerobic, microaerophilic and anaerobic isolates. A most preferred Lactobacillus species is L. fermentum RC-14. Another preferred Lactobacillus species is L. rhamnosus GR-1. Still another preferred lactobacillus species is L. fermentum B-54.

[0024] The preferred strains of lactobacilli within the scope of this invention are anaerobic and microaerophilic isolates.

[0025] By "prebiotic" is meant a nonmetabolized, nonabsorbed substrate that is useful for the host which selectively enhances the growth and/or the metabolic activity of a bacterium or a group of bacteria. A prebiotic also includes a nutrient utilized by lactobacilli or bifidobacteria to stimulate and/or enhance growth of lactobacilli or bifidobacteria relative to pathogenic bacteria.

[0026] Also defined within the present invention are compositions suitable for establishing, maintaining or restoring a healthy gastrointestinal and urogenital flora in females throughout life which comprise one or more Lactobacillus viable whole cells, non-viable whole cells or cell wall fragments and a pharmaceutically acceptable carrier. By "throughout life" is meant in the neonatal period, during childhood and in the pre-menopausal and post-menopausal periods. By "healthy gastrointestinal and urogenital flora" is meant flora that is predominantly colonized by non-pathogenic organisms and where there are no signs or symptoms of infection or disease.

[0027] In a preferred aspect, the Lactobacillus is aerobically, microaerophilically or anaerobically grown and may be selected from the group consisting of Lactobacillus casei, L. acidophilus, L. plantarum, L. fermentum, L. brevis, L. jensenii, L. crispatus, L. rhamnosus, L. reuteri, L. paracasei, L. gasseri, L. cellobiosis, L. delbrueckii, L. helveticus, L. salivarius, L. collinoides, L. buchneri, L. rogosae and L. bifidum.

[0028] The Lactobacillus may be microaerophilically or anaerobically grown and selected from the group consisting of Lactobacillus rhamnosus (GR-1 (ATCC 55826), L. rhamnosus GR-2 (ATCC 55915), L. rhamnosus GR-3 (ATCC 55917), L. rhamnosus GR-4 (ATCC 55916), L. rhamnosus RC-9, L. rhamnosus RC-17 (ATCC 55825), L. casei var alactosus RC-21, L. casei NRC 430, L. casei ATCC 7469, L. rhamnosus 81, L. rhamnosus 76, L. rhamnosus 36W, L. rhamnosus 36g, L. casei RC-65, L. casei RC-15, L. casei 558, L. casei RC-21, L. casei 55, L. casei 8, L. casei 43, L. plantarum RC-12 (ATCC 55895), L. acidophilus RC-25, L. plantarum RC-19, L. jensenii RC-11 (ATCC 55901), L. acidophilus ATCC 4357, L. acidophilus 2099 B, L. acidophilus 2155C, L. acidophilus T-13, L. acidophilus 1807B, L. acidophilus RC-16, L. acidophilus RC-26, L. acidophilus RC-10, L. acidophilus RC-24, L. acidophilus RC-13, L. acidophilus RC-14, L. acidophilus RC-12, L. acidophilus RC-22, L. acidophilus 2099B, L. acidophilus 2155C, L. acidophilus T-13, L. plantarum ATCC 8014, L. plantarum UH 2153, L. plantarum 260, L. plantarum RC-20, L. plantarum 75, L. plantarum RC-6, L. fermentum A-60, L. fermentum B-54 (identical ribotype to RC-14) (ATCC 55920), L. cellobiosis RC-2, L. crispatus 1350B and L. crispatus 2142B.

[0029] In a further embodiment, the present invention describes a method of administering probiotic organisms orally for restoring a healthy urogenital and intestinal flora over the various life cycle stages of women including pregnancy and post-menopause, wherein the flora is dominated by Mobiluncus, Gardnerella, Bacteroides, Fusobacterium, Prevotella, Peptostreptococcus, Porphyromonas, Mycoplasma or group B streptococci, or Escherichia coli, Staphylococcus sp., Enterococcus sp, Klebsiella sp, Pseudomonas sp, Streptococcus sp, Proteus sp, and other Gram negative (such as coliforms) and Gram positive pathogens which cause urinary tract infections and gastrointestinal infections, and yeast including Candida albicans, for example.

[0030] In a preferred embodiment, the Lactobacillus species will produce biosurfactants active against urogenital pathogens including those that cause urinary tract infections, bacterial vaginosis and yeast vaginitis such as Mobiluncus, Gardnerella, Bacteroides, Fusobacterium, Prevotella, Peptostreptococcus, Porphyromonas, Mycoplasma or group B streptococci, or Escherichia coli, Enterococcus sp, Klebsiella sp, Pseudomonas sp, Streptococcus sp, Proteus sp, and yeast.

[0031] In another embodiment, the Lactobacillus species will inhibit growth and adhesion of enteric pathogens to gastrointestinal surfaces including those that cause enteric infections. Such inhibition of enteric pathogens is at least partly due to the production of biosurfactants active against such pathogens including, salmonella, shigella, listeria, campylobacter and clostridium, for example.

[0032] Biosurfactants produced by lactobacilli significantly inhibit the binding of urogenital and gastrointestinal pathogens to surfaces. These biosurfactants contain carbohydrate and proteinaceous compounds. Biochemical analysis using PAGE, affinity chromatography, and amino acid sequencing of biosurfactant produced by L. fermentum RC-14 evidences a 26 kD protein which binds to collagen. This protein, and others which also bind to collagen, play an important role in the colonization by lactobacilli of the vaginal vault. This 26 kD protein is also understood, in accordance with the present invention to play an important role in the protection of the heart against urogenital pathogens.

[0033] Separation and detection of biosurfactants produced by lactobacilli may be preferably accomplished by the SELDI technique (Surface Enhanced Laser desorption/ionization). By "SELDI system" is meant a method which uses protein chips which contain chemically or biologically treated surfaces that specifically interact with or bind the proteins of interest. The protein chips are inserted into a reader which provides an accurate mass profile of the proteins bound to each chip in just a few minutes.

[0034] In a further embodiment the present invention provides a method for selecting lactobacilli and bifidobacteria useful for improving gastrointestinal and urogenital health. Criteria are provided herein for characterizing a selected Lactobacillus or Bifidobacterium as candidates for the contemplated methods and compositions of the present invention. The probiotic organisms will exhibit some or all of the following criteria: an ability to: adhere to vaginal and uroepithelial cells by electrostatic, hydrophobic or specific adhesins including but not limited to a collagen binding protein; pass through the stomach and reach the small and large intestine and urogenital tract; grow and persist in the gastrointestinal and urogenital tracts; inhibit the adhesion of urogenital pathogens including organisms which cause urinary tract infection, bacterial vaginosis and/or yeast vaginitis; coaggregate to form a balanced flora; produce acid and other substances such as hydrogen peroxide and/or bacteriocins and bacteriocin-like compounds which inhibit pathogen growth; produce biosurfactant or related by-products of growth which interfere with adhesion of pathogens to cells and materials; resist antimicrobial agents, such as nonoxynol-9 spermicide; and/or enhance the host's immune function to further maintain a healthy urogenital flora.

[0035] Although this invention is not intended to be limited to any particular mode of application, oral administration of the compositions are preferred. One probiotic organism may be administered alone or in conjunction with a second, different probiotic organism. By "in conjunction with" is meant together, substantially simultaneously or sequentially. The compositions may be administered in the form of tablet, pill or capsule, for example. One preferred form of application involves the preparation of a freeze-dried capsule comprising the composition of the present invention. It has been found that a capsule comprising about 10<sup>sup.9</sup> probiotic organisms is suitable. In accordance with the present invention a capsule may contain one single or two or more different species of probiotic organism(s).

[0036] By "therapeutically effective amount" as used herein is meant an amount of probiotic organism, e.g., lactobacillus, high enough to significantly positively modify the condition to be treated but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. A therapeutically effective amount of lactobacillus will vary with the particular

goal to be achieved, the age and physical condition of the patient being treated, the severity of the underlying disease, the duration of treatment, the nature of concurrent therapy and the specific lactobacillus employed. For example, a therapeutically effective amount of probiotic organism administered to a child or a neonate will be reduced proportionately in accordance with sound medical judgment. The effective amount of lactobacillus will thus be the minimum amount which will provide the desired attachment to epithelial cells. For example, the presence of 5.times.10.sup.9 bacteria, as viable or non-viable whole cells, in 0.05 ml solution of phosphate buffered saline solution, or in 0.05 ml of suspension of agar, or the dry weight equivalent of cell wall fragments, is effective when administered in quantities of from about 0.05 ml to about 20 ml.

[0037] A decided practical advantage is that the probiotic organism, e.g. Lactobacillus, may be administered in a convenient manner such as by the oral, intravenous (where non-viable), or suppository (vaginal or rectal) routes. Depending on the route of administration, the active ingredients which comprise probiotic organisms may be required to be coated in a material to protect said organisms from the action of enzymes, acids and other natural conditions which may inactivate said organisms. In order to administer probiotic organisms by other than parenteral administration, they should be coated by, or administered with, a material to prevent inactivation. For example, probiotic organisms may be co-administered with enzyme inhibitors or in liposomes. Enzyme inhibitors include pancreatic trypsin inhibitor, diisopropylfluorophosphate (DFP) and trasylol. Liposomes include water-in-oil-in-water P40 emulsions as well as conventional and specifically designed liposomes which transport lactobacilli or their by-products to the urogenital surface.

[0038] The probiotic organisms may also be administered parenterally or intraperitoneally. Dispersions can also be prepared, for example, in glycerol, liquid polyethylene glycols, and mixtures thereof, and in oils.

[0039] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol, and the like), suitable mixtures thereof and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion. In many cases it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin..

[0040] Sterile injectable solutions are prepared by incorporating the probiotic organisms in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized probiotic organisms into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

[0041] When the probiotic organisms are suitably protected as described above, the active compound may be orally administered, for example, with an inert diluent or



with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets designed to pass through the stomach (i.e., enteric coated), or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the probiotic organisms may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains about 1.times.10.sup.9 viable or non-viable e.g., lactobacilli per ml.

[0042] The tablets, troches, pills, capsules, and the like, as described above, may also contain the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid, and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil or wintergreen or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the probiotic organism may be incorporated into sustained-release preparations and formulations.

[0043] It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of the probiotic organisms calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly depending on (a) the unique characteristics of the probiotic organism and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such probiotic for the establishment and maintenance of a healthy urogenital flora.

[0044] The probiotic organism is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically or food acceptable carrier in dosage unit form as hereinbefore disclosed. A unit dosage form can, for example, contain the principal active compound in an amount approximating 10.sup.9 viable or non-viable, e.g., lactobacilli, per ml. In the case of compositions containing supplementary ingredients such as prebiotics, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

[0045] By "pharmaceutically-acceptable carrier" as used herein is meant one or more compatible solid or liquid filler diluents, encapsulating substances or foods or drinks, such as yogurt, for example. By "compatible" as used herein is meant that the components of the composition are capable of being comingled without interacting in a manner which would substantially decrease the pharmaceutical efficacy of the total composition under ordinary use situations. The pharmaceutical carrier in accordance with the present invention also is also contemplated to encompass microbial nutrients including specific prebiotics which differentially stimulate the healthy flora, and factors such as antimicrobial compounds, naturally occurring peptides, herbs, vitamins, minerals and plant material, which are active against urogenital pathogens.

[0046] Some examples of substances which can serve as pharmaceutical carriers are sugars, such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethylcellulose, ethylcellulose and cellulose acetates; powdered tragacanth; malt; gelatin; talc; stearic acids; magnesium stearate; calcium sulfate; vegetable oils, such as peanut oils, cotton seed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, manitol, and polyethylene glycol; agar; alginic acids; pyrogen-free water; isotonic saline; and phosphate buffer solution; skim milk powder; as well as other non-toxic compatible substances used in pharmaceutical formulations such as Vitamin C, estrogen and echinacea, for example. Wetting agents and lubricants such as sodium lauryl sulfate, as well as coloring agents, flavoring agents, lubricants, excipients, tableting agents, stabilizers, anti-oxidants and preservatives, can also be present.

[0047] Accordingly, in a preferred form of establishing, maintaining or restoring a healthy gastrointestinal and urogenital flora, the patient is orally administered a therapeutically effective amount of at least one probiotic organism and a pharmaceutically acceptable carrier in accordance with the present invention. A most preferred probiotic organism is a Lactobacillus. Preferably, the Lactobacillus is selected from the group comprising L. rhamnosus, L. casei ss alactosus, L. fermentum and L. brevis. Most preferably, the lactobacillus is either L. rhamnosus GR-1 or L. fermentum B-54 or L. acidophilus RC-14.

[0048] Another preferred composition comprises at least one probiotic organism and a prebiotic and a pharmaceutically acceptable carrier. A preferred prebiotic is insulin.

[0049] The introduction or administration of probiotics to pregnant women in accordance with the present invention will provide protection against infections such as bacterial vaginosis, Group B streptococci, urinary tract infections and others which are capable of adversely affecting the fetus, the newborn and the mother. Accordingly, in a preferred method of establishing a healthy, normal urogenital flora in women before or during pregnancy, a vaginal culture is obtained from the individual and the culture is assayed for the presence of the lactobacilli or bifidobacteria. Selected lactobacilli or bifidobacteria are isolated, purified, grown and optionally frozen and stored (e.g., commercially) for future use by the donor. Alternatively, selected lactobacilli or bifidobacteria are orally or vaginally re-administered in a therapeutically effective amount and form to the donor. In a preferred embodiment at least one probiotic organism is isolated from a donor in need of flora restoration or maintenance. Isolated organisms are resuspended in a pharmaceutical carrier and grown to a concentration permitting the reintroduction or reimplantation of about 10<sup>sup.9</sup> organisms/ml. Reimplanted probiotic organisms are preferably administered about twice a week for about one week to about 52 weeks and most preferably for about one week to about 36 weeks. Orally reintroduced probiotic organisms are preferably administered daily for about one week to about 52 weeks and most preferably for about one week to about 40 weeks.

[0050] The introduction or administration of lactobacilli probiotics to the intestine and passage onto the urogenital tract, and their subsequent production of anti-pathogenic products (e.g., biosurfactants, acids, hydrogen peroxide, bacteriocins) stimulates the immune response against infection and disease and reduces the risk of medical device associated infections. While not wishing to be bound by a particular mechanism, host responses are stimulated which inhibit pathogens and/or create a microenvironment less conducive to pathogen spread in women. Accordingly, in a preferred embodiment of stimulating host responses, a medical device is contacted or coated with lactobacillus at a concentration of about 10<sup>sup.9</sup> organisms/ml prior to introduction into a patient in need of such device. Medical devices contemplated by the present invention include but are not

limited to: intrauterine devices, catheters, stents, drainage lines, intravenous lines, diaphragms, implants, screws, sutures, pads and tampons, for example.

[0051] Although the present invention is not bound by any one theory or mode of operation, it is believed that, at least to some degree, a combination of coaggregation of Lactobacillus and the production by Lactobacillus of one or more inhibitory substances may be responsible for excluding pathogens and/or reducing their numbers at the site of a gastrointestinal or genito-urinary infection.

[0052] From the standpoint of physical exclusion, the attachment of Lactobacillus acts as a block to pathogens by inhibiting access to receptor sites. Although complete exclusion of pathogens theoretically can occur, the most common finding of the results of the present invention is that there is a reduction in pathogen numbers compared to probiotic organisms, e.g., lactobacilli. In other words, although some probiotic organisms may not completely exclude pathogens, they are still capable of interfering with pathogen colonization in vivo.

#### EXAMPLE 1

[0053] The introduction or administration of Lactobacilli restored the urogenital healthy flora and replaced the abnormal biofilm with a healthy biofilm in women having signs of preterm labor.

[0054] Vaginal swabs were collected and analyzed by a Nugent scoring system which grades the flora as normal (score of 0 and dominated by lactobacilli) to 10 (absence of lactobacilli and flora dominated by Gram negative anaerobic bacterial vaginosis pathogens).

[0055] Of 39 women presenting with signs of preterm labor, 23 were diagnosed as having abnormal lactobacilli presence (Nugent scores 4-6) and 16 actually had bacterial vaginosis (B.V.) (Nugent scores >7).

[0056] Oral administration of lactobacilli to restore the lactobacilli flora provided an intervention that lowered the risk of pregnant women going on to deliver their baby preterm. (Table 1)

1TABLE 1

#### PRETERM LABOR STUDY

Group	Sample	@ Vaginal	Clue	Nugent	B
# G.A. Del.					
Discharge	pH	Whiff	cells	Score	Step. Comment
4001	34	+	1		
No	N/A	-ve	-ve	2	-ve
4002	33	+	6	White 4.5	-ve -ve 8 -ve B.V.
4003	32	+	6	White 5.0	-ve -ve 6 -ve
4004	34			White 5.0	-ve -ve
6					-ve
4005	32	+	6	No 5.0	-ve -ve 8 -ve B.V.
4006	34	+	5		
White	6.0			-ve -ve 8	-ve B.V.
4007	32	+	1	No 4.0	+ve -ve 8 -ve
B.V.					

4008 -- -- -- -- --  
 4009 36 + 4 36 + 4 White  
 5.0 -ve -ve 7 -ve B.V.  
 4010 33 + 6 White 4.7 -ve -ve 8 -ve B.V.  
  
 4011 33 Gray 4.7 -ve -ve 6 -ve  
 4012 33 + 2 White 4.0 -ve  
 -ve 6 -ve  
 4013 33 No 5.2 -ve -ve 8 -ve  
 4014 32 + 4 36 No  
 5.0 -ve -ve 8 -ve B.V.  
 4015 30 + 3 30 + 4 No 5.0 -ve -ve 8 -ve  
 B.V.  
 4016 29 + 1 White 4.7 +ve -ve 7 -ve B.V.  
 4017 32  
 White 4.7 -ve -ve 8 -ve B.V.  
 4018 30 No 4.7 -ve -ve 6 -ve ?  
 Strep.  
 4019 33 36 + 1 White 4.7 -ve -ve 1 -ve Lacto.

acidophilus

4020 34 White 4.7 -ve -ve 6 -ve Lactis Lactis

4021 35 +3 White 4.5 -ve -ve 8 -ve B.V.  
 4022 33 + 3 Yellow N/A  
 -ve -ve 4 -ve Lacto.

rhamnosus

4023 -- -- -- --

4024 24 White 5.0 -ve -ve 7 -ve B.V.

4025 32

35 + 2 No 5.3 -ve -ve 4 -ve Lacto

acidophilus

4026

34 + 3 White 5.0 -ve +ve 8 -ve B.V.

4027 32 White 4.7 -ve -ve 3

N/A L.c.

raffinolactis

4028 N/A No 5.8 -ve +ve 3

-ve Lactis Lactis

4029 32 + 2 White 4.4 -ve -ve 2 N/A Lacto.

delb.

delb.

4030 24 + 5 Gray- 4.4 -ve -ve 2 N/A

Lacto. delb.

delb.

4031 23 + 3 26 White 5.0 N/A

-ve 3 N/A

4032 36 + 2 36 + 2 No 4.4 -ve -ve 1 -ve Lacto. delb.

delb.

4033 01/32 No 4.4 -ve -ve 3 N/A Lacto.

crispatus

4034 32 + 3 32 + 5 White 4.2 -ve -ve 0 -ve

4035 30 + 2 No 4.4 -ve -ve 6 N/A

4036 -- -- -- -- --

4037 24 No 4.7 -ve -ve 5 -ve Lacto.

## crispatus

4038 24 + 5 White 5.3 -ve -ve 8 -ve B.V.

4039 36 + 1 No 7.0 -ve

-ve 7 N/A B.V.

4040 30 White 5.0 -ve -ve 7 +ve B.V.

4041

29 White 4.7 -ve -ve 2

Bacterial Morphotype None 1+ 2+  
3+ 4+

Large gram- 4 3 2 1 0  
positive rod

Small gram- 0 1 2 3 4  
negative/variable  
rod

Curved 0 1 1 2 2  
negative/variable  
rod

Score of 0-3 points, Normal; 4-6, intermediate; 7-10 B.V. G.A. =  
gestational age; N/A = not available; ve = vaginal epithelial cells

[0057] Score of 0-3 points, Normal; 4-6, intermediate; 7-10 B.V. G.A.=gestational  
age; N/A=not available; ve=vaginal epithelial cells

## EXAMPLE 2

[0058] SELDI (surface enhanced laser desorption/ionization) was used to separate,  
detect and analyze native proteins at the femtomole level without using labeling or  
time consuming biochemical analytical systems. The SELDI system was used to quickly  
and accurately determine whether clinically important strains of lactobacilli  
expressed collagen binding proteins.

[0059] Four Lactobacillus strains were tested. L. fermentum RC-14 was selected  
because of its potent biosurfactant inhibitory activity against many urogenital  
pathogens. L. rhamnosus GR-1 and 36 also produce biosurfactant, and are also  
inhibitory to enterococci.

[0060] The organisms were grown in MRS broth overnight, harvested and the  
biosurfactant isolated by incubating the organisms for two hours at room  
temperature.

[0061] SELDI System. The resultant data showed the presence of several collagen  
binding proteins in the RC-14 biosurfactant preparation tested with calf skin and  
human placental collagen, particularly at 1.9, 4.7, 9.4, 14.2, 26 and 37 kDa (FIGS.  
2 and 3). Strains GR-1, RC-14 and 36 contained both a 26 kD and 36 kD protein.  
Further analysis-of the biosurfactants showed the presence of sixteen amino acids  
present in varying amounts. (Table 2)

## 2TABLE 2

AMINO ACID COMPOSITION OF HYDROLYZED  
LACTOBACILLUS BIOSURFACTANTSBio- \*\*AMINO ACID COMPOSITION (MOLE  
%)surfactant Asx\* Thr Ser Glx\* Gly Ala Val Met Ile Leu Phe Tyr  
His Lys Arg Pro

36\*\*\* 8.23 3.6 2.98 10.59 8.4 33.98\*\*\*

5.41 1.07 3.58 5.82 1.29 1.97 1.27 5.9 2.39 3.52

GR-1 10.3 7.0

12.3 18.4 18.7 7.86 -- -- 2.02 10.7 -- -- 4.1 -- 1.05 6.94

RC-14

10.4 4.67 5.81 12.5 10.1 8.91 6.19 1.02 3.24 9.5 2.67 3.54 3.64 7.6 5.76

4.52

\* Sample preparation resulted in the deamination of asparagine and glutamine into aspartic acid and glutamic acid, respectively.

\*\* Due to analysis conditions cysteine and tryptophan could not be accurately quantified.

\*\*\* The unlikely high values indicated the presence of free alanine in the sample.

## EXAMPLE 3

[0062] When the patient in need of flora restoration or maintenance is healthy, urogenital organisms are recovered, cultured and the main healthy species isolated and stored. If and when the person has a depleted urogenital flora at some later point in her life, such as during pregnancy or during a urogenital infection, the originally isolated organisms are cultured, and re-implanted vaginally or re-administered orally. This approach will both personalize the therapy and utilize organisms which are known to have been associated with the person's health and recognized as "self"-organisms by their urogenital system at one stage in life.

## EXAMPLE 4

[0063] *L. fermentum* RC-14 has been shown to express a biosurfactant substance capable of inhibiting the adhesion to polystyrene plates of *Gardnerella vaginalis* by 84%, *Bacteroides fragilis* ATCC 25285 by 95%, and Group B streptococcus by 100%, and uropathogenic *Enterococcus faecalis* by up to 90%. Given this data, it is apparent that the *lactobacilli* inhibit organisms responsible for bacterial vaginosis and vaginitis, including *Mobiluncus*, *Fusobacterium*, *Prevotella*, *Peptostreptococcus*, *Porphyromonas* and *Mycoplasma* species.

[0064] Such inhibition of colonization of surfaces of these pathogens is clinically relevant and significant. The only way to eradicate these organisms is the use of antibiotics, and this can have significant side effects particularly for the pregnant mother and fetus. Antimicrobial therapy not only affects the pathogenic organisms, but also impacts the extant vaginal *lactobacilli* and *bifidobacteria*, by depleting such healthy flora. In addition, pathogenic bacteria exist in biofilms, and are able to resist antibiotic treatment and thereby further increasing the

problems of infection. Thus, even after antibiotic therapy to treat bacterial vaginosis, the pathogens still exist for duration of pregnancy, thereby jeopardizing the health of the mother and fetus.

[0065] The contemplated method of administering the probiotics includes daily intake for the first 12 months to 4 years of life, at a time when the male and female newborn is particularly susceptible to urinary infections, which often lead to kidney infection; renal impairment and renal failure. The method of administering the probiotics include daily from puberty to menopause to establish a prolonged healthy urogenital flora during reproductive years, and then altering the composition of the probiotic for daily use post-menopause.

#### EXAMPLE 5

[0066] Naturally occurring substances, such as vitamins, minerals, plants and human peptides have been shown to have activity against uropathogenic organisms. For example, cecropin P1 and Fall-39, vitamin C, cranberry extracts, and other herbs. The critical aspect is the ability of the substances to selectively affect uropathogens as distinct from pathogenic organisms.

[0067] FALL-39 and Cecropin P1 are examples of natural peptides, (Agerberth et al. 1991; Lee et al. 1989) which, according to the mass-spectroscopy the purified FALL-39 fraction had a molecular mass of 4715.23 and the purified cecropin P1 gave a molecular mass of 3338.3, both of which are active against urogenital pathogens (for example *Escherichia coli* HU734, *Enterococcus faecalis* 1131, *Pseudomonas aeruginosa* AK1, *Proteus mirabilis* 28cii, *Klebsiella pneumoniae* 3a, and *Staphylococcus epidermidis* 1938) but not so much against Lactobacillus strains (for example *L. rhamnosus* GR-1, *L. rhamnosus* 81, *L. fermentum* RC-14, *L. fermentum* B-54, and *L. plantarum* RC-20).

[0068] Action of the peptide was considered bactericidal if less than 0.1% of original number of bacteria remained viable following the treatment. Resistant organisms were also plated from the 100  $\mu\text{mol l}^{-1}$  well to confirm presence of any inhibition. Both peptides were found to be active against Gram-negative urogenital pathogens. The mode of action of FALL-39 was found to be bactericidal for *E. coli* and bacteriostatic for both *K. pneumoniae*, and *P. aeruginosa*, whereas Cecropin P1 acted bacteriostatically toward to all three sensitive uropathogens. In addition, we demonstrated that these peptides are active against clinically important strains of Gram-negative urogenital pathogens including previously untested organism *K. pneumoniae*

[0069] When lactobacilli were used as indicator organisms, all strains were highly resistant to Cecropin P1 (MICs > 100  $\mu\text{M}$ ). In a case of FALL-39, four strains, *L. rhamnosus* GR-1, *L. rhamnosus* 81, *L. plantarum* RC-20 and *L. fermentum* RC-14 were resistant, and one strain, *L. fermentum* B-54 was susceptible only at 100  $\mu\text{M}$ . No statistically significant differences were found between viable counts of the resistant strains of lactobacilli in the well with highest concentration of peptides (100  $\mu\text{mol l}^{-1}$ ) and in control wells. FALL-39 appears to act bacteriostatically against *L. fermentum* B-54 (Table 3).

#### 3TABLE 3

Minimal inhibitory concentrations (MIC) of  
FALL-39 and  
cecropin P1 against uropathogenic microorganisms.

MIC ( $\mu\text{mol l}^{-1}$ ) MIC ( $\mu\text{mol l}^{-1}$ )

Organism M)  
FALL-39 Cecropin P1

E. coli 25 1.56  
Ps.  
aeruginosa 12.5 25  
Kl. pneumoniae 50 1.56  
Pr. mirabilis  
>100 >100  
Ent. faecalis >100 >100  
Staph.  
epidermidis >100 >100

## CLAIMS:

What is claimed is:

1. A method of reducing the risk of preterm labor comprising orally administering to a mammalian subject a therapeutically effective amount of at least one probiotic organism and a pharmaceutically acceptable carrier.
2. The method of claim 1 further comprising the administration of a therapeutically effective amount of at least one second probiotic organism.
3. The method of claim 1 wherein said probiotic organism is a Lactobacillus.
4. The method of claim 2 wherein said second probiotic organism is a Bifidobacterium.
5. The method of claims 1 or 2 further comprising the administration of a therapeutically effective amount of a prebiotic.
6. The method of claim 1 wherein said probiotic organism is selected from the group consisting of L. rhamnosus, L. acidophilus, L. fermentum, L. casei, L. reuteri, L. crispatus, L. plantarum, L. paracasei, L. jensenii, L. gasseri, L. cellobiosis, L. brevis, L. delbrueckii, L. helveticus, L. salivarius, L. collinoides, L. buchneri, L. rogosae, or L. bifidum.
7. The method of claim 2 wherein said second probiotic organism is selected from the group consisting of B. bifidum, B. breve, B. adolescentis, or B. longum.
8. An ex vivo method of establishing a healthy gastrointestinal and urogenital flora in a females comprising orally administering to a mammalian subject at least one probiotic organism isolated from said female and a pharmaceutically acceptable carrier.
9. The method of claim 8 wherein said probiotic organism is isolated from the genito-urinary tract of said female.
10. An ex vivo method of restoring healthy gastrointestinal and urogenital flora in



females in need thereof comprising orally administering to a mammalian subject at least one probiotic organism isolated from the individual and a pharmaceutically acceptable carrier.

11. A method of maintaining a healthy gastrointestinal tract in females comprising orally administering to a mammalian subject a therapeutically effective amount of at least one probiotic organism and a pharmaceutically acceptable carrier.

12. The method of claim 11 further comprising the administration of a therapeutically effective amount of at least one second probiotic organism.

13. The method of claim 11 wherein said probiotic organism is a Lactobacillus.

14. The method of claim 12 wherein said second probiotic organism is a Bifidobacterium.

15. The method of claim 11 or 12 further comprising the administration of a therapeutically effective amount of a prebiotic.

16. A pharmaceutical composition comprising at least one probiotic organism and a pharmaceutically acceptable carrier.

17. A method for reducing the risk of bacterial vaginosis and bacterial vaginosis pathogens comprising orally administering to a mammalian subject to a mammalian subject a therapeutically effective amount of at least one probiotic organism and a pharmaceutically acceptable carrier.

18. The method of claim 17 further comprising the administration of a therapeutically effective amount of at least one second probiotic organism.

19. The method of claim 17 wherein said probiotic organism is a Lactobacillus.

20. The method of claim 18 wherein said second probiotic organism is a Bifidobacterium.

21. The method of claims 17 or 18 further comprising the administration of a therapeutically effective amount of a prebiotic.

22. The method of claim 17 wherein said probiotic organism is selected from the group consisting of L. rhamnosus, L. acidophilus, L. fermentum, L. casei, L. reuteri, L. crispatus, L. plantarum, L. paracasei, L. jensenii, L. gasseri, L. cellobiosus, L. brevis, L. delbrueckii, L. helveticus, L. salivarius, L. collinoides, L. buchneri, L. rogosae, or L. bifidum.

23. The method of claim 18 wherein said second probiotic organism is selected from the group consisting of B. bifidum, B. breve, B. adolescentis, or B. longum.

24. A method of stimulating host responses to pathogens comprising contacting a medical device with a therapeutically effective amount of at least one probiotic organism and a pharmaceutically acceptable carrier prior to introduction into a patient in need of such device. a therapeutically effective amount of at least one probiotic organism and a pharmaceutically acceptable carrier.

	EP 1195095	A2 20020410
'OFFENLEGUNGS' DATE:		20020410
APPLICATION INFO.:	EP 2001-307694	20010911
PRIORITY APPLN. INFO.:	GB 2000-24439	20001005

L10 ANSWER 16 OF 16 EUROPATFULL COPYRIGHT 2003 WILA on STN

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

ACCESSION NUMBER: 904784 EUROPATFULL EW 199913 FS OS  
 TITLE: **Probiotic** nutritional preparation.  
 Probiotisches Ernaehrungspraeparat.  
 Preparation nutritionnelle probiotique.  
 INVENTOR(S): Van Hoey-De-Boer, Klaske Anna, Kievitstraat 11, 3443 BD  
 Woerden, NL;  
 Hageman, Robert Johan Joseph, Weidezoo 52, 2742 EV  
 Waddinxveen, NL  
 PATENT ASSIGNEE(S): N.V. Nutricia, Postbus 1, 2700 MA Zoetermeer, NL  
 PATENT ASSIGNEE NO: 923322  
 AGENT: de Bruijn, Leendert C. et al, Nederlandsch Octrooibureau  
 P.O. Box 29720, 2502 LS Den Haag, NL  
 AGENT NUMBER: 19641  
 OTHER SOURCE: ESP1999024 EP 0904784 A1 990331  
 SOURCE: Wila-EPZ-1999-H13-T1b  
 DOCUMENT TYPE: Patent  
 LANGUAGE: Anmeldung in Englisch; Veroeffentlichung in Englisch  
 DESIGNATED STATES: R AT; R BE; R CH; R DE; R DK; R ES; R FI; R FR; R GB; R  
 GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE  
 PATENT INFO.PUB.TYPE: EPA1 EUROPATISCHE PATENTANMELDUNG  
 PATENT INFORMATION:

	PATENT NO	KIND DATE
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	EP 904784	A1 19990331
'OFFENLEGUNGS' DATE:		19990331
APPLICATION INFO.:	EP 1997-202900	19970922

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<input type="checkbox"/>	L7	L6 and (capsule or tablet)	6
<input type="checkbox"/>	L6	L5 and adolescentis	8
<input type="checkbox"/>	L5	L4 and (acidophilus or casei or fermentum or saivaroes or brevis or leichmannii or plantarum or cellobiosius)	53
<input type="checkbox"/>	L4	L3 and (mucopolysaccharide? or pectin? or chitin or agar or carrage\$)	60
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<input type="checkbox"/>	L1	probiotic\$	1174

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NEWS	6	AUG 18	Data available for download as a PDF in RDISCLOSURE
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NEWS	10	SEP 22	DIPPR file reloaded
NEWS	11	DEC 08	INPADOC: Legal Status data reloaded
NEWS	12	SEP 29	DISSABS now available on STN
NEWS	13	OCT 10	PCTFULL: Two new display fields added
NEWS	14	OCT 21	BIOSIS file reloaded and enhanced
NEWS	15	OCT 28	BIOSIS file segment of TOXCENTER reloaded and enhanced
NEWS	16	NOV 24	MSDS-CCOHS file reloaded
NEWS	17	DEC 08	CABA reloaded with left truncation
NEWS	18	DEC 08	IMS file names changed
NEWS	19	DEC 09	Experimental property data collected by CAS now available in REGISTRY
NEWS	20	DEC 09	STN Entry Date available for display in REGISTRY and CA/CAPLUS
NEWS	21	DEC 17	DGENE: Two new display fields added
NEWS	22	DEC 18	BIOTECHNO no longer updated
NEWS	23	DEC 19	CROPU no longer updated; subscriber discount no longer available
NEWS EXPRESS	NOVEMBER 14 CURRENT WINDOWS VERSION IS V6.01c, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003		
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=> s probiotic  
L1 5018 PROBIOTIC

=> s l1 and prebiotic  
L2 301 L1 AND PREBIOTIC

=> s l2 and (bifidobacteria and lactobacillus)  
L3 71 L2 AND (BIFIDOBACTERIA AND LACTOBACILLUS)

=> s l2 and (bifidobacteria or lactobacillus)  
L4 202 L2 AND (BIFIDOBACTERIA OR LACTOBACILLUS)

=> s l4 and (muocoploysaccharide# or pectin# or chitin or agar or carragenan)  
L5 62 L4 AND (MUOCOPLOYSACCHARIDE# OR PECTIN# OR CHITIN OR AGAR OR CARRAGENAN)

=> s l5 and (acidophilus or casei or fermentum or salivaroes or brevis or leichmannii or plantarum or cellobiosius)  
L6 45 L5 AND (ACIDOPHILUS OR CASEI OR FERMENTUM OR SALIVAROEES OR BREVIS OR LEICHMANNII OR PLANTARUM OR CELLOBIOSIUS)

=> s l6 and (Bifidobacteria adolescentis)  
L7 0 L6 AND (BIFIDOBACTERIA ADOLESCENTIS)

=> s l6 and (B adolescentis)  
L8 3 L6 AND (B ADOLESCENTIS)

=> s l8 and (capsule# or tablet#)\  
MISSING OPERATOR TABLET#)\  
The search profile that was entered contains terms or  
nested terms that are not separated by a logical operator.

=> s l8 and (capsule# or tablet#)  
L9 2 L8 AND (CAPSULE# OR TABLET#)

=> d l9 1-2 ibib abs

L9 ANSWER 1 OF 2 USPATFULL on STN  
ACCESSION NUMBER: 2003:213220 USPATFULL

TITLE: **Probiotic/prebiotic** composition and delivery method  
INVENTOR(S): Monte, Woodrow C., Riverton, NEW ZEALAND  
PATENT ASSIGNEE(S): Corpak MedSystems, Inc. (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003147857	A1	20030807
APPLICATION INFO.:	US 2002-68750	A1	20020205 (10)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Squire, Sanders & Dempsey L.L.P., Intellectual Property Dept., Two Renaissance Square, 40 North Central Avenue, Suite 2700, Phoenix, AZ, 85004-4498		
NUMBER OF CLAIMS:	59		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	1 Drawing Page(s)		
LINE COUNT:	752		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A **prebiotic**, composition comprising a **probiotic** and **prebiotic**, and method of delivering a **probiotic**, **prebiotic** or composition directly into the intestinal tract of a mammal are disclosed. The **probiotic** is any beneficial bacteria and the **prebiotic** is a substance beneficial to a **probiotic**. Most preferably, the **prebiotic** includes a mucopolysaccharide. The method preferably involves delivering the **probiotic**, **prebiotic** or composition via a delivery tube, such as an enteral feeding tube, directly to a position downstream of the stomach, most preferably to the jejunum.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 2 OF 2 USPATFULL on STN

ACCESSION NUMBER: 2003:172727 USPATFULL  
TITLE: Oral administration of **lactobacillus** for the maintenance of health in women during pregnancy and at other life stages, to reduce the risk of urogenital diseases  
INVENTOR(S): Reid, Gregor, London, CANADA  
Bruce, Andrew W., Uxbridge, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003118571	A1	20030626
APPLICATION INFO.:	US 2002-317666	A1	20021210 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2000-579307, filed on 25 May 2000, ABANDONED		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-135955P	19990525 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	SCULLY SCOTT MURPHY & PRESSER, PC, 400 GARDEN CITY PLAZA, GARDEN CITY, NY, 11530	
NUMBER OF CLAIMS:	24	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	3 Drawing Page(s)	
LINE COUNT:	838	

AB The present invention provides methods and compositions for the oral administration of **Lactobacillus** and/or other **probiotic** organisms, such as *Bifidobacterium*, for establishment and maintenance of a healthy urogenital flora. The invention also provides methods and compositions to reduce the risk of disease, including onset of preterm labor due to vaginal and cervical infection. The invention also provides

ex vivo methods of restoring healthy gastrointestinal and vaginal flora.

=> d his

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FILE 'CAPLUS, USPATFULL, JAPIO, MEDLINE, EUROPATFULL, BIOSIS' ENTERED AT 13:26:08 ON 19 DEC 2003

L1 5018 S PROBIOTIC  
L2 301 S L1 AND PREBIOTIC  
L3 71 S L2 AND (BIFIDOBACTERIA AND LACTOBACILLUS)  
L4 202 S L2 AND (BIFIDOBACTERIA OR LACTOBACILLUS)  
L5 62 S L4 AND (MUOCOPLOYSACCHARIDE# OR PECTIN# OR CHITIN OR AGAR OR  
L6 45 S L5 AND (ACIDOPHILUS OR CASEI OR FERMENTUM OR SALIVAROEES OR B  
L7 0 S L6 AND (BIFIDOBACTERIA ADOLESCENTIS)  
L8 3 S L6 AND (B ADOLESCENTIS)  
L9 2 S L8 AND (CAPSULE# OR TABLET#)

=> s l6 and (capsule# or tablet#)

L10 16 L6 AND (CAPSULE# OR TABLET#)

=> d l10 1-16 ibib abs

L10 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:609851 CAPLUS

DOCUMENT NUMBER: 139:154902

TITLE: Probiotic/prebiotic composition  
and delivery method

INVENTOR(S): Monte, Woodrow C.

PATENT ASSIGNEE(S): Corpak Medsystems, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 9 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003147857	A1	20030807	US 2002-68750	20020205
PRIORITY APPLN. INFO.:			US 2002-68750	20020205

AB A **prebiotic**, compn. comprising a **probiotic** and **prebiotic**, and method of delivering a **probiotic**, **prebiotic** or compn. directly into the intestinal tract of a mammal are disclosed. The **probiotic** is any beneficial bacteria and the **prebiotic** is a substance beneficial to a **probiotic**. Most preferably, the **prebiotic** includes a mucopolysaccharide. The method preferably involves delivering the **probiotic**, **prebiotic** or compn. via a delivery tube, such as an enteral feeding tube, directly to a position downstream of the stomach, most preferably to the jejunum.

L10 ANSWER 2 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2003:306035 USPATFULL

TITLE: Bifidobacterium in the treatment of inflammatory disease

INVENTOR(S): Collins, John Kevin, Doughcloyne, IRELAND

O'Sullivan, Gerald Christopher, Cork, IRELAND

O'Mahony, Liam, Cork, IRELAND

Shanahan, Fergus, Kinsale, IRELAND

PATENT ASSIGNEE(S): Enterprise Ireland (Trading as Bioresearch Ireland and National University of Ireland, Cork. (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003215467	A1	20031120
APPLICATION INFO.:	US 2003-388652	A1	20030317 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2001-903681, filed on 13 Jul 2001, PENDING Continuation of Ser. No. WO 2000-IE8, filed on 17 Jan 2000, UNKNOWN		

	NUMBER	DATE
PRIORITY INFORMATION:	IE 1999-990033	19990115
	IE 1999-990782	19990920
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	JACOBSON HOLMAN PLLC, 400 SEVENTH STREET N.W., SUITE 600, WASHINGTON, DC, 20004	
NUMBER OF CLAIMS:	54	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	13 Drawing Page(s)	
LINE COUNT:	1316	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		

AB A strain of Bifidobacterium isolated from resected and washed human gastrointestinal tract is significantly immunomodulatory following oral consumption in humans. The strain is useful in the prophylaxis and/or treatment of undesirable inflammatroy activity, especially gastrointestinal inflammatory activity such as inflammatory bowel disease or irritable bowel syndrome. The inflammatory activity may also be due to cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 3 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2003:243808 USPATFULL

TITLE: Bifidobacterium in the treatment of inflammatory disease

INVENTOR(S): Collins, John Kevin, Duncloyne, IRELAND  
O'Sullivan, Gerald Christopher, Cork, IRELAND  
O'Mahony, Liam, Cork, IRELAND  
Shanahan, Fergus, Kinsale, IRELAND

PATENT ASSIGNEE(S): Enterprise Ireland (Trading as Bioresearch Ireland and National University of Ireland, Cork. (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003170217	A1	20030911
APPLICATION INFO.:	US 2003-376602	A1	20030303 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2001-903681, filed on 13 Jul 2001, PENDING Continuation of Ser. No. WO 2000-IE8, filed on 17 Jan 2000, UNKNOWN		

	NUMBER	DATE
PRIORITY INFORMATION:	IE 1999-990033	19990115
	IE 1999-990782	19990920
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	JACOBSON HOLMAN PLLC, 400 SEVENTH STREET N.W., SUITE 600, WASHINGTON, DC, 20004	
NUMBER OF CLAIMS:	54	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	13 Drawing Page(s)	
LINE COUNT:	1321	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
AB A strain of Bifidobacterium isolated from resected and washed human		



gastrointestinal tract is significantly immunomodulatory following oral consumption in humans. The strain is useful in the prophylaxis and/or treatment of undesirable inflammatory activity, especially gastrointestinal inflammatory activity such as inflammatory bowel disease or irritable bowel syndrome. The inflammatory activity may also be due to cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 4 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2003:237315 USPATFULL  
TITLE: Storage and delivery of micro-organisms  
INVENTOR(S): McGrath, Susan, New Haven, CT, UNITED STATES  
McHale, Anthony Patrick, Antrim, UNITED KINGDOM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003165472	A1	20030904
APPLICATION INFO.:	US 2003-221271	A1	20030221 (10)
	WO 2001-GB1062		20010312

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2000-5839	20000310
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Paul M Booth, Intellectual Property Department, Heller Ehrman White & McAuliffe, 101 Orchard Ridge Drive Suite 300, Gaithersburg, MD, 20787-1917	
NUMBER OF CLAIMS:	30	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	9 Drawing Page(s)	
LINE COUNT:	1596	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB We describe a method of delivering a micro-organism to an animal, the method comprising providing a formulation comprising a micro-organism suspended in or on a matrix; providing a feed stream for the animal; detaching micro-organisms from the matrix; and entraining detached micro-organisms into the feed stream. An apparatus for delivering a micro-organism to an animal is also described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 5 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2003:213220 USPATFULL  
TITLE: **Probiotic/prebiotic** composition and delivery method  
INVENTOR(S): Monte, Woodrow C., Riverton, NEW ZEALAND  
PATENT ASSIGNEE(S): Corpak MedSystems, Inc. (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003147857	A1	20030807
APPLICATION INFO.:	US 2002-68750	A1	20020205 (10)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Squire, Sanders & Dempsey L.L.P., Intellectual Property Dept., Two Renaissance Square, 40 North Central Avenue, Suite 2700, Phoenix, AZ, 85004-4498		
NUMBER OF CLAIMS:	59		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	1 Drawing Page(s)		
LINE COUNT:	752		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A **prebiotic**, composition comprising a **probiotic** and

**prebiotic**, and method of delivering a **probiotic**, **prebiotic** or composition directly into the intestinal tract of a mammal are disclosed. The **probiotic** is any beneficial bacteria and the **prebiotic** is a substance beneficial to a **probiotic**. Most preferably, the **prebiotic** includes a mucopolysaccharide. The method preferably involves delivering the **probiotic**, **prebiotic** or composition via a delivery tube, such as an enteral feeding tube, directly to a position downstream of the stomach, most preferably to the jejunum.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 6 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2003:172727 USPATFULL

TITLE: Oral administration of **lactobacillus** for the maintenance of health in women during pregnancy and at other life stages, to reduce the risk of urogenital diseases

INVENTOR(S): Reid, Gregor, London, CANADA  
Bruce, Andrew W., Uxbridge, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003118571	A1	20030626
APPLICATION INFO.:	US 2002-317666	A1	20021210 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2000-579307, filed on 25 May 2000, ABANDONED		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-135955P	19990525 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	SCULLY SCOTT MURPHY & PRESSER, PC, 400 GARDEN CITY PLAZA, GARDEN CITY, NY, 11530	
NUMBER OF CLAIMS:	24	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	3 Drawing Page(s)	
LINE COUNT:	838	

AB The present invention provides methods and compositions for the oral administration of **Lactobacillus** and/or other **probiotic** organisms, such as Bifidobacterium, for establishment and maintenance of a healthy urogenital flora. The invention also provides methods and compositions to reduce the risk of disease, including onset of preterm labor due to vaginal and cervical infection. The invention also provides ex vivo methods of restoring healthy gastrointestinal and vaginal flora.

L10 ANSWER 7 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2003:165452 USPATFULL

TITLE: **Probiotic lactobacillus casei** strains

INVENTOR(S): Collins, John Kevin, Doughcloyne, IRELAND  
O'sullivan, Gerald Christopher, Cork, IRELAND  
O'Mahony, Liam, Cork, IRELAND  
Shanahan, Fergus, Kinsale, IRELAND  
Kiely, Barry, Passage West, IRELAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003113306	A1	20030619
APPLICATION INFO.:	US 2002-201917	A1	20020725 (10)

NUMBER	DATE
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PRIORITY INFORMATION: IE 2001-20010715 20010726  
 IE 2001-20010706 20010726  
 IE 2001-20010700 20010726  
 IE 2001-20010699 20010726  
 IE 2001-20010712 20010726

DOCUMENT TYPE: Utility  
 FILE SEGMENT: APPLICATION  
 LEGAL REPRESENTATIVE: JACOBSON HOLMAN, PROFESSIONAL LIMITED LIABILITY  
 COMPANY, 400 SEVENTH STREET. N.W., WASHINGTON, DC,  
 20004

NUMBER OF CLAIMS: 47  
 EXEMPLARY CLAIM: 1  
 NUMBER OF DRAWINGS: 3 Drawing Page(s)  
 LINE COUNT: 1350

AB A **Lactobacillus casei** strain or a mutant or variant thereof isolated from resected and washed human gastrointestinal tract is significantly immunomodulatory following oral consumption in humans. In particular a **Lactobacillus casei** strain, AH101, AH104, AH111, AH112 or AH113 or mutants or variants are thereof are useful in the prophylaxis and/or treatment of inflammatory activity especially undesirable gastrointestinal inflammatory activity, such as inflammatory bowel disease or irritable bowel syndrome.

L10 ANSWER 8 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2003:134078 USPATFULL  
 TITLE: **Probiotic bifidobacterium strains**  
 INVENTOR(S): Collins, John Kevin, Doughcloyne, IRELAND  
 O'Sullivan, Gerald Christopher, Cork, IRELAND  
 O'Mahony, Liam, Cork, IRELAND  
 Shanahan, Fergus, Kinsale, IRELAND  
 Kiely, Barry, Passage West, IRELAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003092163	A1	20030515
APPLICATION INFO.:	US 2002-201940	A1	20020725 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	IE 2001-20010711	20010726
	IE 2001-20010710	20010726
	IE 2001-20010709	20010726
	IE 2001-20010714	20010726
	IE 2001-20010713	20010726
	IE 2001-20010717	20010726
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	JACOBSON HOLMAN, PROFESSIONAL LIMITED LIABILITY COMPANY, 400 SEVENTH STREET N.W., WASHINGTON, DC, 20004	
NUMBER OF CLAIMS:	46	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	3 Drawing Page(s)	
LINE COUNT:	1318	

AB A Bifidobacterium strain, AH208, AH209, AH210, AH211, AH212 or AH214 or mutants or variants thereof are useful in the prophylaxis and/or treatment of inflammatory activity especially undesirable gastrointestinal inflammatory activity, such as inflammatory bowel disease or irritable bowel syndrome.

L10 ANSWER 9 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2003:133464 USPATFULL  
 TITLE: **Probiotic lactobacillus salivarius**  
 strains

INVENTOR(S): Collins, John Kevin, Doughcloyne, IRELAND  
O'Sullivan, Gerald Christopher, Cork, IRELAND  
O'Mahony, Liam, Cork, IRELAND  
Shanahan, Fergus, Kinsale, IRELAND  
Kiely, Barry, Passage West, IRELAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003091549	A1	20030515
APPLICATION INFO.:	US 2002-205318	A1	20020726 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	IE 2001-20010708	20010726
	IE 2001-20010707	20010726
	IE 2001-20010705	20010726
	IE 2001-20010702	20010726
	IE 2001-20010701	20010726

DOCUMENT TYPE: Utility  
FILE SEGMENT: APPLICATION  
LEGAL REPRESENTATIVE: JACOBSON HOLMAN, PROFESSIONAL LIMITED LIABILITY  
COMPANY, 400 SEVENTH STREET N.W., WASHINGTON, DC, 20004  
NUMBER OF CLAIMS: 45  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 3 Drawing Page(s)  
LINE COUNT: 1360

AB A *Lactobacillus* salivarius strain, AH102, AH103, AH105, AH109  
or AH110 or mutants or variants thereof are useful in the prophylaxis  
and/or treatment of inflammatory activity especially undesirable  
gastrointestinal inflammatory activity, such as inflammatory bowel  
disease or irritable bowel syndrome.

L10 ANSWER 10 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2002:12056 USPATFULL  
TITLE: Bifidobacterium in the treatment of inflammatory  
disease

INVENTOR(S): Collins, John Kevin, Duncloyne, IRELAND  
O'Sullivan, Gerald Christopher, Cork, IRELAND  
O'Mahony, Liam, Cork, IRELAND  
Shanahan, Fergus, Kinsale, IRELAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002006432	A1	20020117
APPLICATION INFO.:	US 2001-903681	A1	20010713 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2000-IE8, filed on 17 Jan 2000, UNKNOWN		

	NUMBER	DATE
PRIORITY INFORMATION:	IE 1999-990033	19990115
	IE 1999-990782	19990920
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	JACOBSON, PRICE, HOLMAN & STERN, PROFESSIONAL LIMITED LIABILITY COMPANY, 400 SEVENTH STREET N.W., WASHINGTON, DC, 20004	
NUMBER OF CLAIMS:	54	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	13 Drawing Page(s)	
LINE COUNT:	1316	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A strain of *Bifidobacterium* isolated from resected and washed human  
gastrointestinal tract is significantly immunomodulatory following oral

consumption in humans. The strain is useful in the prophylaxis and/or treatment of undesirable inflammatory activity, especially gastrointestinal inflammatory activity such as inflammatory bowel disease or irritable bowel syndrome. The inflammatory activity may also be due to cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 11 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2001:139178 USPATFULL

TITLE: Encapsulated multifunctional biologically active food component, process for its production and its use

INVENTOR(S): Jager, Martin, Gauersheim, Germany, Federal Republic of  
Haber, Bernd, Mainz, Germany, Federal Republic of  
Kunz, Benno, Meckenheim, Germany, Federal Republic of  
Strater, Stephanie, Roesrath-Hasbach, Germany, Federal Republic of  
Weissbrodt, Jenny, Wiehl, Germany, Federal Republic of  
Bollinger, Hartmut, Neuler, Germany, Federal Republic of  
Brendle, Hans-Georg, Ellwangen, Germany, Federal Republic of

PATENT ASSIGNEE(S): Bache, Georg, Buehlertann, Germany, Federal Republic of  
Nutrinova Nutrition Specialties & Food Ingredients GmbH  
(non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001016220	A1	20010823
APPLICATION INFO.:	US 2000-747850	A1	20001221 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1999-19962427	19991222
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	ProPat LLC, Suite 400, 6230 Fairview Rd., Charlotte, NC, 28210	
NUMBER OF CLAIMS:	11	
EXEMPLARY CLAIM:	1	
LINE COUNT:	502	

AB The invention relates to a multifunctional encapsulated biologically active food component consisting of a core which comprises at least one dietary fiber, which core is surrounded by at least one biologically active substance, in which the core and the biologically active substance(s) is (are) surrounded by one or more shell-forming substance(s).

L10 ANSWER 12 OF 16 EUROPATFULL COPYRIGHT 2003 WILA on STN

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

ACCESSION NUMBER: 1344458 EUROPATFULL EW 200338 FS OS

TITLE: **Probiotic** delivery system.  
System zur Verabreichung von Probiotika.  
Systeme d'administration de composes probiotiques.

INVENTOR(S): Ubbink, Johan Bernard, Route de Vers-chez-les-Blancs 2,  
La Claise-aux-Moines, 1073 Savigny, CH;  
Schaer-Zammaratti, Prisca, Stettbachstrasse 193, 8051  
Zuerich, CH;  
Cavadini, Christoph, Ch. de Paudille 26, 1801 Le  
Mont-Pelerin, CH

PATENT ASSIGNEE(S): Societe des Produits Nestle S.A., P.O.Box 353, 1800  
Vevey, CH

PATENT ASSIGNEE NO: 229228  
AGENT: Wavre, Claude-Alain et al., 55, avenue Nestle, 1800  
Vevey, CH  
AGENT NUMBER: 27271  
OTHER SOURCE: MEPA2003070 EP 1344458 A1 0015  
SOURCE: Wila-EPZ-2003-H38-T3a  
DOCUMENT TYPE: Patent  
LANGUAGE: Anmeldung in Englisch; Veroeffentlichung in Englisch  
DESIGNATED STATES: R AT; R BE; R CH; R CY; R DE; R DK; R ES; R FI; R FR; R  
GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R  
SE; R TR; R AL; R LT; R LV; R MK; R RO; R SI  
PATENT INFO.PUB.TYPE: EPA1 EUROPAEISCHE PATENTANMELDUNG  
PATENT INFORMATION:

	PATENT NO	KIND DATE
	EP 1344458	A1 20030917
'OFFENLEGUNGS' DATE:		20030917
APPLICATION INFO.:	EP 2002-5607	20020312

L10 ANSWER 13 OF 16 EUROPATFULL COPYRIGHT 2003 WILA on STN

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

ACCESSION NUMBER: 1300472 EUROPATFULL EW 200315 FS OS  
TITLE: A method for testing the effect of nutrients on  
gastrointestinal colonisation resistance of humans.  
Verfahren zur Pruefung der Wirkung von Nahrungsmittel,  
eine Resistenz gegen Kolonisation durch Bakterien  
zuerzeugen.  
Methode d'analyse de la resistance envers une  
colonisation des intenstins cause par l'alimentation.  
INVENTOR(S): Bodee-Oudenhoven, Ingeborg Marie Jacqueline, Saltshof  
3020, 6604 GL Wijchen, NL;  
Van der Meer, Roelof, Witte de Withstraat 37, 6712 HA  
Ede, NL  
PATENT ASSIGNEE(S): Stichting Top-Instituut Voedselwetenschappen, Diedenweg  
20, P.O. Box 557, 6700 AN Wageningen, NL  
PATENT ASSIGNEE NO: 3270561  
AGENT: Jorritsma, Ruurd et al., Nederlandsch Octrooibureau  
Scheveningseweg 82 P.O. Box 29720, 2502 LS Den Haag, NL  
AGENT NUMBER: 69541  
OTHER SOURCE: MEPA2003028 EP 1300472 A1 0011  
SOURCE: Wila-EPZ-2003-H15-T1a  
DOCUMENT TYPE: Patent  
LANGUAGE: Anmeldung in Englisch; Veroeffentlichung in Englisch  
DESIGNATED STATES: R AT; R BE; R CH; R CY; R DE; R DK; R ES; R FI; R FR; R  
GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R  
SE; R TR; R AL; R LT; R LV; R MK; R RO; R SI  
PATENT INFO.PUB.TYPE: EPA1 EUROPAEISCHE PATENTANMELDUNG  
PATENT INFORMATION:

	PATENT NO	KIND DATE
	EP 1300472	A1 20030409
'OFFENLEGUNGS' DATE:		20030409
APPLICATION INFO.:	EP 2001-203745	20011002

L10 ANSWER 14 OF 16 EUROPATFULL COPYRIGHT 2003 WILA on STN

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

ACCESSION NUMBER: 1260227 EUROPATFULL EW 200248 FS OS  
TITLE: Lipoteichoic acid from lactic acid bacteria and its use  
to modulate immune responses mediated by gram-negative  
bacteria, potential pathogenic gram-positive bacteria.  
Lipoteichonsaeure aus Milchsaeurebakterien sowie dessen

Verwendung zur Modulierung der durch gram-negative, potenziell pathogene gram-positive Bakterien induzierte Immunantwort.  
L'acide lipoteichoique des bacteries lactiques et son utilisation pour moduler des responses immunitaires induites par des bacteries a gram negatif, gram positif.

INVENTOR(S): Vidal, Karine, Chemin de Beree 56, 1010 Lausanne, CH;  
Granato, Dominique, La Dioramade, Rte de Cretaz, 1091 Grandvaux, CH;  
Donnet-Hughes, Anne, Rue Chatel-St-Denis 29B, 1806 Saint-Legier, CH;  
Corthesy-Theulaz, Irene, Chemin du Polny 34C, 1066 Epalinges, CH

PATENT ASSIGNEE(S): SOCIETE DES PRODUITS NESTLE S.A., Case postale 353, 1800 Vevey, CH

PATENT ASSIGNEE NO: 229220

OTHER SOURCE: BEPA2002099 EP 1260227 A1 0022

SOURCE: Wila-EPZ-2002-H48-T1b

DOCUMENT TYPE: Patent

LANGUAGE: Anmeldung in Englisch; Veroeffentlichung in Englisch

DESIGNATED STATES: R AT; R BE; R CH; R CY; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE; R TR; R AL; R LT; R LV; R MK; R RO; R SI

PATENT INFO.PUB.TYPE: EPA1 EUROPÄISCHE PATENTANMELDUNG

PATENT INFORMATION:

PATENT NO	KIND	DATE
EP 1260227	A1	20021127
		20021127
EP 2001-201958		20010523

'OFFENLEGUNGS' DATE: 20021127

APPLICATION INFO.: EP 2001-201958 20010523

L10 ANSWER 15 OF 16 EUROPATFULL COPYRIGHT 2003 WILA on STN

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

ACCESSION NUMBER: 1195095 EUROPATFULL EW 200215 FS OS

TITLE: Food products with antimicrobial lactic acid bacteria.  
Nahrungsmittel mit antimikrobiellen Milchsäurebakterien.  
Produits alimentaires avec des bacteries d'acide lactique antimicrobiennes.

INVENTOR(S): Griggs, Christopher William, 36 Templars Firs, Wootton Bassett, Wiltshire SN4 7EW, GB;  
Fooks, Laura Janine, 14 Fernhill Close, Blackwater, Camberley, Surrey GU17 9HD, GB;  
Gibson, Glenn Robinson, Food Microb. Science Unit, Univ. of Reading, PO Box 226, Whiteknights, Reading RG6 6AP, GB

PATENT ASSIGNEE(S): St. Ivel Limited, Station Road, Wootton Bassett, Swindon, Wiltshire SN4 7EF, GB

PATENT ASSIGNEE NO: 888582

AGENT: Daniels, Jeffrey Nicholas et al., Page White & Farrer 54 Doughty Street, London WC1N 2LS, GB

AGENT NUMBER: 69921

OTHER SOURCE: BEPA2002031 EP 1195095 A2 0032

SOURCE: Wila-EPZ-2002-H15-T3a

DOCUMENT TYPE: Patent

LANGUAGE: Anmeldung in Englisch; Veroeffentlichung in Englisch

DESIGNATED STATES: R AT; R BE; R CH; R CY; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE; R TR; R AL; R LT; R LV; R MK; R RO; R SI

PATENT INFO.PUB.TYPE: EPA2 EUROPÄISCHE PATENTANMELDUNG

PATENT INFORMATION:

PATENT NO	KIND	DATE

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File: PGPB

Jan 31, 2002

PGPUB-DOCUMENT-NUMBER: 20020012689

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020012689 A1

TITLE: Method of hydration; infusion packet system(s), support member(s), delivery system(s), and method(s); with business model(s) and Method(s)

PUBLICATION-DATE: January 31, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Stillman, Suzanne Jaffe	Los Angeles	CA	US	

US-CL-CURRENT: 424/439; 424/738, 514/54

## CLAIMS:

I claim:

1. An infusion packet for preparing a functional nutraceutical beverage comprising: an aliquot of water-soluble dietary fiber; and a water permeable membrane that envelops said fiber and is sealed so as to form a packet wherein said fiber cannot penetrate said membrane until said packet is immersed in water.

2. The infusion packet of claim 1 further comprising ingredients selected from the group consisting of probiotics, prebiotics, flavorings, encapsulated substances, coloring material, amino acids, antioxidants, enzymes, nutraceuticals and dietary supplements.

3. The infusion packet of claim 1, wherein the water soluble dietary fiber is selected from the group consisting of plant mucilage, plant gums, dextrins, maltodextrins, galactomannans, arabanogalactans, beta glucans, cellulose ethers, pectins, pectic material, water-soluble hemicellulose, inulin, alginates, agar, carrageenan, psyllium, guar gum, gum traganth, gum karya, gum ghatti, gum acacia, gum arabic, partially hydrolyzed products thereof and mixtures thereof.

4. The infusion packet of claim 1, wherein said water-soluble fiber is selected to satisfy simultaneously both hydration requirements and fiber requirements when consumed.

5. The infusion packet of claim 1 formulated for managing constipation.

6. A method of managing bowel regularity comprising the step of ingesting a quantity of a solution prepared by placing the infusion packet of claim 1 into water or an aqueous solution.

7. A method of managing hemorrhoids comprising the step of ingesting a quantity of a solution prepared by placing the infusion packet of claim 1 into water or an



aqueous solution.

8. A method of avoiding assimilation of toxic bowel compounds comprising the step of ingesting a quantity of a solution prepared by placing the infusion packet of claim 1 into water or an aqueous solution.

9. The infusion packet of claim 1 formulated for management of diabetes.

10. The infusion packet of claim 1 formulated for management of obesity.

11. The infusion packet of claim 1 formulated to stimulate the immune system.

12. The infusion packet of claim 1 formulated for appetite suppression.

13. The infusion packet of claim 1 formulated for lowering serum cholesterol levels.

14. The infusion packet of claim 1 formulated for management of diarrhea.

15. A method for preparing a functional nutraceutical beverage comprising the steps of: providing an infusion packet claim 1; and immersing said infusion packet in water whereby said fiber and any other ingredients are dissolved and penetrate the membrane to make a functional nutraceutical beverage.

16. An infusion packet for preparing a beverage of the type wherein an aliquot of water-soluble ingredients are surrounded by a water permeable membrane that envelops said ingredients and is sealed so as to form a packet wherein said ingredients cannot penetrate said membrane until said packet is immersed in water and a tag that is tethered to said packet characterized by having the tag structured so as to perform a function other than identification of the contents or origin of the infusion packet.

17. The infusion packet of claim 16, wherein the tag is formed so as to carry out a function selected from the group consisting of acting as a card in a card game, acting as a piece of a puzzle, acting as a toy, acting as a charm for a bracelet, acting as an ornament, acting as an aroma source, acting as a clip and forming part of a contest.

18. The infusion packet of claim 16, wherein the tag is formed so as to form one member of a related set so that the tags may be collected to complete the set.

19. The infusion packet of claim 18, wherein a plurality of infusion packets constituting related members of the set are dispensed together in a single package.

20. The infusion packet of claim 19, wherein the package together with the tags forms a game.

21. An infusion packet for preparing a beverage of the type wherein an aliquot of water-soluble ingredients are surrounded by a water permeable membrane that envelops said ingredients and is sealed so as to form a packet wherein said ingredients cannot penetrate said membrane until said packet is immersed in water and a tag that is tethered to said packet characterized by having the permeable membrane structured so as to carry out an additional function selected from the group consisting of allowing the contents to be clearly visible, forming a figure or toy, showing indicia, showing indicia in response to contact with a liquid, dissolving after contacting liquid, releasing embedded encapsulations, releasing

color into the liquid and forming an edible confection after contacting liquid.

22. The infusion packet of claim 21, wherein said membrane is formed with perforations forming a patterns and said pattern is revealed when the packet is placed in liquid.

23. The infusion packet of claim 21, wherein said membrane is formed from an impermeable substance and a tool is provided to create perforations to allow penetration of liquid.

24. The infusion packet of claim 21, wherein said membrane is formed so as to contain more than one compartment so that incompatible ingredients remain separated.

25. An infusion packet for preparing a beverage of the type wherein an aliquot of water-soluble ingredients are surrounded by a water permeable membrane that envelops said ingredients and is sealed so as to form a packet wherein said ingredients cannot penetrate said membrane until said packet is immersed in water and a tag that is tethered to said packet characterized by having an additional support member surrounding the infusion packet or attached to one or a plurality of diffusion packets.

26. The infusion packet of claim 25, wherein the support member forms a toy.

27. The infusion packet of claim 26, wherein the support member connects to a drinking straw.

28. The infusion packet of claim 25, wherein the support member connects at least two infusion packets to form a compound infusion packet.

29. The infusion packet of claim 25, wherein the support member grasps the infusion packet and acts as a handle.

30. An infusion packet for preparing a beverage of the type wherein an aliquot of water-soluble ingredients are surrounded by a water permeable membrane that envelops said ingredients and is sealed so as to form a packet wherein said ingredients cannot penetrate said membrane until said packet is immersed in water said packet characterized by ingredients selected from the group consisting of probiotics, prebiotics, encapsulated substances, amino acids, antioxidants, and enzymes.

31. An infusion packet for preparing a beverage of the type wherein an aliquot of water-soluble ingredients are surrounded by a water permeable membrane that envelops said ingredients and is sealed so as to form a packet wherein said ingredients cannot penetrate said membrane until said packet is immersed in water and a tag that is tethered to said packet, said packet characterized having a size and shape allowing insertion through a neck of a bottle, the packet deforming in response to liquid so that the packet cannot be withdrawn through the neck.

32. The infusion packet of claim 31, wherein the tag is adhesive allowing attachment to an outer surface of the bottle.

33. The infusion packet of claim 31, wherein the tag is impregnated with a fragrance.